VA COOPERATIVE STUDIES PROGRAM # 424

Clinical **O**utcomes **U**tilizing **R**evascularization and **A**ggressive Dru**G** **E**valuation

Protocol Amendment No.: 3

THIS PROTOCOL REPRESENTS A CHANGE TO THE REVISED FEBRUARY 1999 COURAGE PROTOCOL AND SHOULD BE SUBMITTED TO YOUR INSTITUTIONAL REVIEW BOARD/ETHICAL REVIEW COMMITTEE

Please send a copy of your protocol amendment approval from your institutional review board/ethical review committee to the West Haven Coordinating Center and to the Co-Chairman's Office in Syracuse.

This amendment contains two parts: 1) Inclusion of patients with "classic" or "definite" angina in whom non-invasive testing for myocardial ischemia cannot be readily obtained and 2) a definition of "classic" or "definite" angina.

1) INCLUSION OF PATIENTS WITH "CLASSIC" OR "DEFINITE" ANGINA

There are potentially many COURAGE-eligible patients with “classic” or “definite” angina who have angiographically-significant proximal coronary artery disease (CAD), but who have proceeded directly to the cardiac catheterization laboratory without first having had objective evidence of myocardial ischemia documented by an abnormal resting ECG or non-invasive laboratory testing (exercise or pharmacologic). In many instances, the decision to proceed directly to coronary angiography has been dictated by referral practice patterns and the expectation that diagnostic coronary angiography would be obtained expediently to assess the presence or absence of abnormal coronary anatomy.

Presently, the COURAGE Trial inclusion criteria mandate the documentation of myocardial ischemia; COURAGE-eligible patients must have either demonstrable ST-T wave changes in two or more contiguous ECG leads at rest, or have objective evidence of inducible ischemia during exercise or pharmacologic vasodilator stress (exercise-induced ST-segment deviation of at least 0.1 mV; a reversible perfusion defect or wall motion abnormality during stress myocardial perfusion imaging or echocardiography).

In order to broaden patient enrollment and to include appropriate patients with symptomatic CAD who may be suitable candidates for percutaneous coronary intervention (PCI) even in the absence of objective findings of ischemia, we propose to modify the COURAGE Trial inclusion criteria in selected instances whereby patients with subjective symptoms of “classic”, or “definite”, angina (please refer to Op Memo #

26) may be trial-eligible without objective findings of myocardial ischemia if they meet a more stringent definition of angiographic stenosis in the setting of multivessel CAD.

The following revised definition for trial inclusion will be used for COURAGE-eligible patients who have symptomatic CAD (the principal target population of patients who would be expected to benefit from PCI) but who have no objective evidence of myocardial ischemia.

All three of the criteria listed below must be met for a patient to be considered COURAGE Trial-eligible:

- The patient must have symptoms of "classic", or "definite", angina, as defined in Op Memo # 26. In brief, patients must display (in the opinion of the investigator or operator) convincing symptomatology of exertional or rest angina that meets the cardinal criteria (character, site & distribution, provocation and duration) described originally by Heberden and Wood, and adopted as the definition of "classic", or "definite", angina in the recently-published ACC/AHA Guidelines on both the Management of Chronic Stable Angina and Unstable Angina/Non-ST-Segment Elevation Acute Coronary Syndromes; **and**

- The patient must have a measured 70% or greater angiographic stenosis (caliper-measured or quantitatively-measured) of a proximal epicardial coronary artery that, in the opinion of the operator/investigator, is the culprit vessel responsible for the ischemic syndrome; **and**

- There must be angiographic documentation of significant stenosis (50% or greater) in another coronary artery in additional to the 70% or greater "culprit stenosis". Thus, the patient must have multivessel (2-3 vessel) CAD.

In summary, the standard COURAGE Trial criteria of defining objective evidence of myocardial ischemia and angiographic CAD (50% or greater in a proximal epicardial coronary artery) remain the principal inclusion criteria for patient recruitment.

For those potentially COURAGE-eligible patients with symptoms of "classic" or "definite" angina who are referred from outlying hospitals or from referring physicians with the stated expectation that they would proceed directly to diagnostic coronary angiography, this change in the trial inclusion criteria should facilitate the enrollment of patients with multivessel CAD who have at least a measured 70% stenosis of a proximal coronary artery.

2) DEFINITION OF "CLASSIC" OR "DEFINITE" ANGINA FOR ENROLLMENT OF PATIENTS IN WHOM NON-INVASIVE TESTING FOR MYOCARDIAL ISCHEMIA CANNOT BE READILY OBTAINED

For the purposes of enrolling eligible patients with "classic", or "definite", angina without objective signs of myocardial ischemia in the COURAGE Trial, we will adhere to the

definitions as described in the ACC/AHA/ACP-ASIM Guidelines for the Management of Patients with Chronic Stable Angina[1].

We will subdivide patients according to whether the presentation is unstable angina (UA) or chronic stable angina (CSA), as described below.

I. Presentations of Unstable Angina (UA):

There are three principal presentations of UA: 1) rest angina (angina commencing when the patient is at rest), 2) new-onset severe angina, and 3) increasing angina (Table 1).

Table 1. Three Principal Presentations of UA

Rest angina	Angina occurring at rest and prolonged, usually > 20 minutes.
New-onset angina	New-onset angina of at least CCS Class III severity.
Increasing angina	Previously diagnosed angina that has become distinctly more frequent, longer in duration, or lower in threshold (i.e., increased by $\geq$ 1 CCS class to at least CCS Class III severity).

Angina severity will be classified according to the Canadian Cardiovascular Society (CCS) system (Table 2).

Table 2. Grading of Angina Pectoris According to CCS Classification[2]

Class	Description of Stage
I	"Ordinary physical activity does not cause…angina," such as walking or climbing stairs. Angina occurs with strenuous, rapid, or prolonged exertion at work or recreation.
II	"Slight limitation of ordinary activity." Angina occurs on walking or climbing stairs rapidly; walking uphill; walking or stair climbing after meals; in cold, in wind, or under emotional stress; or only during the few hours after awakening. Angina occurs on walking > 2 blocks on the level and climbing > 1 flight of ordinary stairs at a normal pace and under normal conditions.
III	"Marked limitations of ordinary physical activity." Angina occurs on walking 1 to 2 blocks on the level and climbing 1 flight of stairs under normal conditions and at a normal pace.
IV	Inability to carry on any physical activity without discomfort-anginal symptoms may be present at rest."

II. Presentations of Chronic Stable Angina (CSA):

Angina is characterized as a deep, poorly localized chest or arm discomfort that is reproducibly associated with physical exertion or emotional stress and is relieved promptly (i.e., < 5 min) with rest and/or the use of sublingual nitroglycerin (NTG). Patients with UA may have discomfort that has all of the qualities of typical angina except that the episodes are more severe and prolonged, may occur at rest, or may be precipitated by less exertion than previously. Some patients may have no chest discomfort but present solely with jaw, neck, ear, arm, or epigastric discomfort. If these symptoms have a clear relationship to exertion or stress or are relieved promptly with NTG, they should be considered equivalent to angina. Occasionally, such "anginal equivalents" that occur at rest are the mode of presentation of a patient with UA, but without the exertional history, it may be difficult to recognize the cardiac origin. Other difficult presentations of the patient with UA include those without any chest (or

equivalent) discomfort. Isolated unexplained new-onset or worsened exertional dyspnea is the most common anginal equivalent symptom, especially in older patients; others include nausea and vomiting, diaphoresis, and unexplained fatigue. Elderly patients, especially women with ACS, often present with atypical angina.

III. Features of "Classic", or "Definite" Angina:

There are four cardinal manifestations of "classic" or "definite" angina: character, site and distribution, provocation, and duration. Patients with "definite" angina typically have substernal or retrosternal chest discomfort (pressure, squeezing, tightness, burning) that may also be located in the midepigastric area. The discomfort can radiate to the arm (upper or lower), neck, jaw, ear or teeth, and is typically precipitated by physical exertion, stress, meals, emotion, etc., are frequently stereotypic in a given patient, and may occur with both provocation and at rest, or with minimal activity. The duration of angina is usually minutes (unless it is prolonged rest angina indicative of an acute coronary syndrome), and the discomfort typically subsides promptly with rest (or cessation of the offending activity), or following sublingual nitroglycerin.

Features that are *not* characteristic of myocardial ischemia include the following:

- Pleuritic pain (i.e., sharp or knife-like pain brought on by respiratory movements or cough)
- Primary or sole location of discomfort in the middle or lower abdominal region
- Pain that may be localized at the tip of 1 finger, particularly over the left ventricular (LV) apex
- Pain reproduced with movement or palpation of the chest wall or arms
- Constant pain that lasts for many hours
- Very brief episodes of pain that last a few seconds or less
- Pain that radiates into the lower extremities

[1]Gibbons RJ, Chatterjee K, Daley J, et al. ACC/AHA/ACP-ASIM guidelines for the management of patients with chronic stable angina. J Am Coll Cardiol 1999;33:2092-197

[2]Campeau L. Grading of angina pectoris (letter). Circulation 1976;54:522-3

Approved by:

_____	_____	_____
William E. Boden, MD	Robert A. O'Rourke, MD	Pamela M. Hartigan, PhD
Study Co-Chairman	Study Co-Chairman	Study Statistician

3 November 2000